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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/786,533	01/21/1997	MARCUS A. HORWITZ	120-243	5368

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EXAMINER
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ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 04/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
08/786,533	Horwitz et al
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-28* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *2, 4*
4) ☒ Interview Summary (PTO-413) Paper No(s). *24 25*
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. After review and reconsideration, the finality of the rejection of Paper no. 23, mailed Oct 2, 2002, is withdrawn in light of the following rejections.

2. Claims 1-3, 6-8, 11, 12, 14, 15, 17, 18, 20, 21, 23 and 25 have been amended. Claims 1-28 are pending and under consideration.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

New Grounds of Rejection

4. Claims 1-10 comprise the limitation of Il-12 as an adjuvant. It is noted that the prior applications which are relied upon for an earlier effective filing date than the instant filing date of January 21, 1997 do not disclose the use of Il-12 as an adjuvant. Furthermore, application 08/156,358, was filed November 23, 1993, and at that time Il-12 was not recognized as an adjuvant. Accordingly, claims 1-10 are given the priority date of the instant application.

5. Claims 6 and 13, 16, 19 and 22 are objected to because of the following informalities: Claim 6 contains the typographical error "ad"; claim 13 contains the typographical error of "siad"; claims 19 and 22 contain the typographical error "homolgos"; claim 16 contains the typographical error "tubercuolsis". Appropriate correction is required.

6. Claims 11, 12 and 13 are objected to under 37 CFR 1.75 as being a substantial duplicate of claims 14, 15 and 16. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. The recitation of an intended use does not impart patentable distinctness to a product. Therefore, without the incorporation of further limitations, claim 11 encompasses the same agents as claim 14. See MPEP § 706.03(k).

7. Claims 1, 2, 3, 6, 7, 8, 11, 12, 14, 15, 17, 18, 20-25 and 27-28 are objected to as not complying with 1.821(d) of the Sequence Rules and Regulations. The claims are drawn to the 30,

32, 16, 58, 23.5 and 24 KD proteins which are disclosed by the specification to be SEQ ID NO:35, 36, 92, 93, 94 and 95. When the claims of a patent application discusses a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of the Sequence Rules and Regulations, reference must be made to the sequence by use of the assigned identifier, in the text of the description or claims of the patent application. Appropriate correction is required.

8. The specification is objected to as not complying with 1.821(d) of the Sequence Rules and Regulations. When the specification of a patent application discusses a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph (c) of the Sequence Rules and Regulations, reference must be made to the sequence by use of the assigned identifier, in the text of the description or claims of the patent application. See: page 22, line 18, page 24, line 32, page 26, lines 23, 27, 30, 32, 33, page 27, lines 2, 7, 10, 13, 17, 19, 21, 22, 25, 28, page 28, lines 5, 6, 11, 12, page 35, lines 1, 14, page 36, line 23, page 37, lines 3, 5, 13, 24, 828, page 38, line 11, 23, 31, 32, 33, page 39, lines 1, 16, 18, 26, 29, page 40, lines 11, 23, 31, page 41, lines 1, 16, page 42, lines 1, 6, 23, page 43, lines 1, 16, 18, 26, page 46, line 5, 15, page 49, line 5, 6, page 55, lines 7, 10, page 57, line 11, 16, 17, 22, 27, 30, 33, page 58, line 31, page 59, line 7, page 61, line 20, page 62, lines 14, 22, page 63, lines 4, 8, 10, page 64, lines 10, 14, 17, page 76, line 17, page 82, lines 27, 28, page 85, lines 4-8, 10, 12, 13, page 90, line 4, page 93, lines 2-7, page 96, lines 10, 11, 20, 30, page 98, line 29 to page 99, line 6, page 103, lines 15-18, 24, 25, 32, 34, page 104, line s 6, 23, 30, 31, page 105, line 2, 9, 13, 26, page 106, lines 18, 22, 28, 34, 35, page 107, line 15, 16, 19, 20, 23, 28, page 109, lines 4, 5, 7, 15, 20, 30, 31, 33, 35, page 110, lines 3, 7, 11, 14, 16, 17, 20, 24, 29, 30, 33, page 111, lines 4, 6, 10, 12, 16, 18, 23, 29, 31, 32, page 116, lines 17, 23, 26, page 118, line 21, page 119, lines 21, 24, 39, page 120, line 33, page 121, line 8, 11, 14, page 123, lines 25, 28, page 127, lines 2, 3, 13, 25, 26, page 128, line 17, and page 129, lines 3 and 27. Appropriate correction is required.

9. Claims 1-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 6, 11, 14, 17, 20 and 23 recite "M tuberculosis 110 KD protein, 80 KD protein, 71 KD protein". It is unclear if the limitation "M tuberculosis" is to be applied to all the proteins subsequent to the 110 KD protein in light of the preamble which states "pathogen of the genus mycobacterium". For purpose of examination, both alternatives will be considered. Claims 3 and 8 recite "M tuberculosis 32 KD protein, 30 KD protein and 16 KD protein". It is unclear if the limitation of "M tuberculosis is to be applied to the 30 KD protein and the 16 KD protein. For purpose of examination, both alternatives will be considered. Further, it is unclear if the "30 KD protein is representative of the antigen 85 complex, sometimes referred to as the 30-31-32 KD complex, which comprises a 30 KD protein, a 31 KD protein and a 31.5 KD protein, wherein the 31 KD protein is also known as p32 (Nagai et al, Infection and Immunity, 1991, Vol. 59, pp. 372-382, page 372, second column, first full paragraph, and table 1 under the CIE designations of 85A, 85B and 85C). For purpose of examination, the "30 KD protein" will be alternatively read as comprised in the antigen 85 complex, and separated from said complex, in view that claims drawn to the 32A KD protein have been made dependent on claims drawn to the 30 KD protein.

The recitation of "32A KD protein" in claims 3, 8, 13, 16, 19 and 22 lacks proper antecedent basis in claims 1, 6, 12, 15, 18 and 21, respectively. Further, it is unclear how the 32A KD protein differs from the 32 KD protein.

Claims 1, 6, 11, 14, 17, 20 and 23 are vague and indefinite in the reliance upon a molecular weight as the only means to characterize the claimed proteins and methods reliant thereupon. Other proteins having the same molecular weight but different amino acid sequences could read on the claimed invention. Further, the claims are vague and indefinite in the recitation of "KD" without the specific method used to measure the molecular weights. It is well know in the art that proteins can display widely differing apparent molecular weights as a result of

complex physical and chemical interactions with buffer and gel matrix constituents, therefore the actual method used to define the molecular weight is a necessary part of defining molecular weight.

The recitation of "pSMT3" in claim 26 renders the claim vague and indefinite because pSMT3 is a laboratory designation coined by the inventor and unknown in the art.

The recitation of "subunits thereof" in claims 1, 6, 11, 13, 14, 16 is vague and indefinite and it is unclear if a subunit is synonymous with a fragment of the recited proteins, or if a subunit is a separate protein within the recited proteins which can be obtained from the recited proteins by chemical means. For purpose of examination, both alternatives will be considered.

The recitation of "majorly abundant" in claims 1, 2, 3, 6, 7, 8, 11, 12, 14, 15, 17, 18, 20, 21, 23 and 25 renders the claims vague and indefinite. The specification defines "majorly abundant" on page 14, lines 4-21 as a relative term identifying extracellular products released in the greatest quantity by the pathogens of interest. "Thus, out of the total exemplary 4 mg/L total output of extracellular product for M tuberculosis grown under normal or heat-shock conditions, approximately fifteen to twenty (alone or in combination) of the hundred or so known extracellular products will constitute approximately ninety percent of the total quantity". Firstly, ninety percent of the total quantity has ben set forth as an exemplary amount not a limiting amount. Secondly, it is not possible to ascertain the relative contribution of any individual protein of the "fifteen to twenty" which taken together constitute 90% of the extracellular protein. It is unclear if each protein constitutes an equal portion of the 90% or if the relative amounts of the extracellular proteins can vary within the 90% of the total extracellular proteins. Thirdly, the profile of extracellular proteins resulting from M tuberculosis is recognize to change with the strain of tuberculosis used and the culture conditions and be dependent upon added factors, such as zinc and age of the culture (see for example, Abou-Zeid et al, J of General Microbiology, 1988, vol. 134, pp. 531-538, especially pages 534-537, under the heading "Discussion"). Thus, the

profile of majorly abundant extracellular proteins are variable rendering the claims indefinite by dependence upon an object which is variable.

Claims 13, 16, 19 and 22 contain the term "inversions". It is unclear if this refers to the inversion of the bonding of the amino acid to the peptide chain, as in a peptoid linkage versus a peptide linkage, or if this refers to the exchange of amino acids within the peptide.

10. Claims 1-28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(A) As drawn to new matter

Applicant has amended claims 1-3, 6, 7, 8, 11, 12, 14, 15, 17, 18, 20, 21, 23 and 25 to incorporate the limitation "secreted" into the qualifications of the claimed majorly abundant extracellular products and methods reliant thereupon, in order to overcome the prior art rejections. The insertion of this limitation for the entire Markush groups recited in claims 1, 6, 11, 14, 17, 20, and 23 represents new matter for the following reasons. Applicant has drawn the examiners attention to page 18 at lines 9-14, which recite "Further, the use of a few well defined molecules corresponding to the majorly abundant secretory or extracellular products greatly reduces the risk of adverse side effects associated with conventional vaccines" and page 22, lines 5-8 which recite "However, it should be emphasized that the present invention is not restricted to combinations of secretory or extracellular products. For example, several alternative experimental protocols demonstrate the capacity of a single abundant extracellular product to induce mammalian protective immunity in accordance with the teachings of the present invention". This is insufficient support for the limitation of "secreted" as applied to all of the recited antigens. Page 22, lines 15-18 identifies the claimed 30 KD protein as a secretory protein. However, the 71 KD protein, identified in the specification on page 34, lines 14-32, as the 71 KD heat shock

protein is not a secreted protein (Rambukkana et al, Infection and Immunity, 1992, Vol. 60, pp. 4517-4527, first column, lines 1-4), but an extracellularly abundant protein harvested from older cell cultures which have accumulated proteins from dead cells. The specification fails to point out which of the other claimed proteins are secreted versus extracelluarly abundant. Therefore, one of skill in the art would conclude that the specification does not provide support for the amendment of "secreted" to describe all of the claimed proteins.

(B) As drawn to written description

Claims 1-5 and 11-16 are drawn to agents comprising at least a portion of at least one majorly abundant extracellular product comprising m tuberculosis 110 KD protein, 80 KD protein, 71 KD protein, 58 KD protein, 45 KD protein, 30 KD protein, 24 KD protein, 23.5 KD protein, 23 KD protein, 16 KD protein, 14 KD protein, 12 KD protein, and respective analogs, homologs and subunits thereof. It is noted that the recitation of intended use in claims 1, 11 and 14 has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). The claims are considered to be drawn to the recited proteins in the Markush group and would be anticipated by the prior art disclosure of the proteins apart from the intended use. Further, for the reasons given in the rejection under 112, second paragraph above, the limitation of "M tuberculosis is not being applied to all the antigens because the metes and bounds of claims 1, 11 and 14 are unclear. Claim 23 is drawn to processes for producing said majorly abundant extracellular products. Therefore, the claims are drawn to a large genus of proteins comprising any extracellular protein of apparent molecular weight of 80 KD, 71 KD, 58 KD, 45 KD, 30 KD, 24 KD, 23.5 KD, 23 KD, 16 KD, 14 KD and 12 KD in addition to any extracellular protein of M tuberculosis having an apparent molecular

weight of 110 KD obtained by any means of molecular weight determination including both denaturing conditions and non-denaturing conditions. Claims 24, 25, 27 and 28 are drawn to processes for producing said majorly abundant extracellular product of a 30 KD protein. When given the broadest reasonable interpretation, claims 24, 25, 27 and 28 read on any extracellular M tuberculosis protein, wherein the molecular weight is measured by any method. The specification lacks teachings wherein structural attributes of the claimed proteins can be used to distinguish members of the genus from proteins which are not members of the genus. Amendment of the claims to recite sequence identifiers where possible will partially obviate this rejection. However, it is noted that a sequence has not been provided for the 110 KD, 80 KD, 71 KD, 45 KD, 23 KD, 14 KD or 12 KD proteins. Further, claims 1, 11, 14 are drawn to "respective analogs, homologs and subunits thereof". Neither the specification nor the claims limits the number of structural alterations which are encompassed by "analogs, homologs and subunits thereof", nor does the specification define what constitutes an analog. It would be reasonable to conclude that analogs, homologs and subunits thereof do not need to exhibit the same apparent molecular weight as the 110 KD, 80 KD, 71 KD, 58 KD, 45 KD, 30 KD, 24 KD, 23.5 KD, 23 KD, 16 KD, 14 KD and 12 KD proteins. Thus, when given the broadest reasonable interpretation the claims read on any protein which is abundantly extracellular. Claims 13 and 16 are drawn to agents comprising epitopes selected from the group consisting of SEQ ID NO:106, 107, 110, 114, 115, 118, 120, 122, 123, 124, 126, 127, 134, 135 and 136 in addition to "analogs, homologs, and subunits thereof including single or multiple amino acid substitutions, deletions, insertions and inversion". Neither the specification nor the claims limits the number of structural alterations encompassed by claims 13 and 16, therefore they read on any fragment of an extracellular protein of M tuberculosis having an apparent molecular weight of 30 KD as assessed by any physical method of measuring molecular weight. The specification provides a written description of SEQ ID NO:35, 36, 92, 93, 94 and 95 which are the 30 KD, 32 KD, 16 KD, 58 KD, 23.5 KD and 24 KD proteins. Because the claimed genus is highly variant, the disclosure of SEQ ID NO:35, 36, 92, 93, 94 and

95 is insufficient to describe the claimed genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the claimed genus. Thus applicant as not in possession of the claimed genus.

Further, the methods of claims 6, 17 and 20 are drawn to immunizing a host against an infectious pathogen of the genus Mycobacterium and detecting the presence of an immune response against a pathogen of the genus Mycobacterium. The genus "Mycobacterium" is a large genus encompassing all pathogenic mycobacteria such as leprae, bovis, avium-intracellulare, avium, lepraemurium, scrofulaceum, chelonae, paratuberculosis, haemophilum, xenopi, ulcerans, smegmatis, phlei, marinum, kansasii, foruitum, as well as tuberculosis. Claims 6-10, 17-19 and 20-22 are reliant on the genus of proteins which lack adequate written description for the reasons set forth above,. Because the proteins lack adequate written description and because the genus of "mycobacterium" is large, the disclosure of methods reliant upon SEQ ID NO:35, 36, 92, 93, 94 and 95 for the immunization of a host against a specific member of the "mycobacterium" genus, M tuberculosis, and the detecting of a specific member of the "mycobacterium" genus, M tuberculosis, is insufficient to describe the genus of proteins relied upon for the instant method claims. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the claimed genus. Thus applicant as not in possession of the claimed genus.

Claims 23, 24, 27 and 28 are drawn in part to a process of producing the products of M tuberculosis 110 KD protein and the 80 KD, 71 KD, 45 KD, 23 KD, 14 KD and 12 KD proteins comprising the transformation of a host cell with a vector . However, neither an amino acid sequence, nor a polynucleotide sequence encoding said amino acid sequence has been provided for these proteins. In The Regents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated the description of a genus is achieved by the recitation of a representative number of

DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...requires a precise definition, such as by structure, formula, chemical name, or physical properties", not a mere wish or plan for obtaining the claimed chemical invention. Therefore, the recitation of a "vector" for the production of proteins, without the disclosure of amino acid sequences, is an inadequate description of the vectors upon which the method claims rely. One of skill in the art would conclude that applicant was not in possession of said vectors at the effective filing date.

11. Claims 23-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for vectors which are commercially available or reproduced from the art, and extracellular products in which the amino acid sequence has been disclosed, does not reasonably provide enablement for the pSMT3 vector or the nucleic acids encoding the extracellular products of the M tuberculosis 110 KD protein or nucleic acid molecules encoding the 71 KD, 45 KD and 12 KD proteins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The specification does not provide deposit information or sequence information to guarantee that one of skill in the art can reproduce the exact claimed vector. One of skill in the art would not know how to make the claimed vector as its DNA sequence has not been disclosed. Further, one of skill in the art would be subject to undue experimentation in the identification of all proteins which have the recited molecular weight and all polynucleotides encoding said proteins. One of skill in the art would be subject to undue experimentation in order to identify clones expressing all possible claimed proteins wherein said polynucleotides or proteins have not been described by sequence or enabled by a deposit of a cell line producing the recombinant polynucleotides.

12. Claims 11 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Abou-Zeid et al (Journal of General Microbiology, 1988, Vol. 134, pp. 531-538, reference HQ of the IDS filed March 17, 1997) Claim 11 is drawn to a vaccinating agent comprising at least one immunodominant epitope of at least one majorly abundant extracellular product selected from the group consisting of the M tuberculosis 110 KD protein, 80 KD protein, 71 KD protein, 58 KD protein, 45 KD protein, 30 KD protein, 24 KD protein, 23.5 KD protein, 23 KD protein, 16 KD protein, 14 KD protein, 12 KD protein, and respective analogs, homologs and subunits thereof. Claim 14 is drawn to an immunodiagonsitc agent having the same limitations as claim 11. It is noted that the claims are vague and indefinite for the reasons set forth in the rejection under 112, second paragraph above, and the limitations of intended use do not influence the patentability of a product, for the reasons set forth above. Abou-Zeid et al disclose the M tuberculosis proteins of 71 KD, 23 KD, 14 KD and 12 KD which are present as secreted proteins in the culture medium of M tuberculosis (page 533, table 1), thus fulfilling the limitation of extracellularly abundant proteins.

13. Claims 11, 14, 23 and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Joliff et al (Molecular Microbiology, 1992, Vol. 6, pp. 2349-2362). The limitations of claims 11 and 14 are set forth above. Claim 23 is drawn to a process for producing a majorly abundant extracellular product selected from the group consisting of the M tuberculosis 110 KD protein, 80 KD protein, 71 KD protein, 58 KD protein, 45 KD protein, 30 KD protein, 24 KD protein, 23.5 KD protein, 23 KD protein, 16 KD protein, 14 KD protein, 12 KD protein, and respective analogs, homologs and subunits thereof, said process comprising the steps of transforming a host cell with a vector to form a transformed cell, and culturing said transformed cell to produce said majorly abundant extracellular products. Claim 25 embodies the method of claim 23 with the additional step of recovering the products so produced.

Joliff et al disclose a protein of 71 KD which is a majorly abundant extracellular product of C glutamicium (page 2350, column 1, first full paragraph) and a homolog of the secreted 85 B protein of M tuberculosis (page 2357, first column, lines 9-11 under the heading "Sequence similarities between the PS1 and the Mycobacterium protein of antigen 85 complex"). The 85B protein of M tuberculosis has a molecular weight of 30 KD as evidenced by Table 1 in Nagai et al (Infection and Immunity, 1991, Vol. 59, pp. 372-382). Joliff et al disclose a process for producing the recombinant protein in E coli and the recovery of said protein (page 2352 to 2353, under the heading "Identification of protein extracts from the recombinant lysogens" and page 2353, under the heading "subcloning the csp1 gene in pUN121").

14. Claims 11-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Daugelat et al (Journal of Infectious Diseases, 1992, Vol. 166, pp. 186-190). The specific limitations of claims 11 and 14 are set forth above. Claim 12 is drawn to the vaccinating agent of claim 12 wherein the product is the M tuberculosis 30 KD protein. Claim 13 embodies the vaccinating agent of claim 13 wherein the immunodominant epitope is selected from the M tuberculosis 32 KD subunit comprising the peptides of SEQ ID NO:106, 107, 110, 114, 115, 118, 120, 122, 124, 126, 127, 34, 135, 136 and respective analogs, homologs, and subunits thereof including single or multiple amino acid substitutions, deletions, insertions and inversions. Claims 15 and 16 have the same limitations as claims 12 and 13.

Daugelat et al disclose the secreted proteins of M tuberculosis (page 187, figure 1). Daugelat et al disclose that the 32 KD antigen was included in these proteins (page 190, lines 11-14) and thus fulfilling the specific limitation of claims 13 and 16, drawn to the 32 KD protein. Daugelat et al do not disclose the agent consisting of the peptides of SEQ ID NO:106, 107, 110, 114, 115, 118, 120, 122, 124, 126, 127, 34, 135, 136, however, claims 11 and 14 are drawn to a vaccinating agent comprising "at least one immunodominant epitope" and thus read on the full length 32 KD protein which would comprise the recited SEQ ID NO.

15. Claims 11-16 and 20-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Nagai et al (Infection and Immunity, 1991, Vol. 59, pp. 372-383, reference AR of the IDS filed March 17, 1997). The limitations of claims 11-16 are recited above. Claim 20 is drawn to a method for detecting the presence of an immun response in a mammal against a pathogen of the genus Mycobacterium, said method comprising the steps of : providing at least one immunodominant epitope of at least one majorly abundant secreted extracellular product selected from the group consisting of M tuberculosis 110 KD protein, 80 KD protein, 71 KD protein, 58 KD protein, 45 KD protein, 30 KD protein, 24 KD protein, 23.5 KD protein, 23 KD protein, 16 KD protein, 14 KD protein, and 12 KD protein and respective analogs, homologs and subunits thereof; administering said at least one immunodominant epitope to said mammal and measuring the resultant immune response. Claim 21 embodies the method of claim 20 wherein said at lest one majorly abundant secreted extracellular product is M tuberculosis 30 KD protein. Claim 22 embodies the method of claim 21 wherein said at least one immunodominant epitope is selected from the group consisting of M tuberculosis 32 KD protein subunits having the amino acid sequences of SEQ ID NO:106, 107, 110, 114, 115, 118, 120, 122, 124, 126, 127, 34, 135, 136 and respective analogs, homologs and subunits thereof, including single or multiple amino acid substitutions, deletions, insertions and inversions.

Nagai et al disclose an 80 KD protein, a 41 KD protein, 31.5, 31, and 30 KD proteins, 27, 26 and 25 KD proteins, and 18, 15 14 and 12 KD proteins which are major protein antigens found in M tuberculosis culture fluid. Nagai et al disclose that the 41 KD, 31 KD, 31.5 KD, 27 KD, 26 KD, 18 KD and 15 KD proteins are secreted proteins. Nagai et al discloses the claimed 80 KD, 30, 14 and 12 KD proteins. It is noted that the specification does not provide a definition of an "analog". In this case , the meaning of the term is the ordinary usage in the art. The art defines analogue as a chemical compound that is similar in structure to another but different in composition in the matter of the placement or presence of some functional groups. Nagai discloses a 41 KD protein, a 31.5 KD protein, a 27 KD protein, a 26 KD protein, a 18 KD protein

and a 15 KD protein which are either the same as the claimed 45 KD protein, 30 KD protein, 24 KD protein, 23.5 KD protein, 23, KD protein and 16 KD protein, but differ in apparent molecular weight due to experimental differences in the molecular weight determination, or analogs to said proteins as the disclosed agents are all amino acid sequences, but differ from the 45 KD, 30 KD, 24 KD, 23.5 KD, 23 KD and 16 KD proteins in the presence and placement of amino acids. Also, it is reasonable to conclude that the 31 KD protein disclosed by Nagai et al is the same as the claimed 32A KD protein as Nagai et al disclosed an alternate name for said protein is P32 and 85A, and cites the reference number 7 which is "Purification, characterization and identification of a 32 KD protein antigen of M bovis."

Nagai et al disclose a method of detecting the presence of an immune response in a mammal against M tuberculosis comprising the administration of the above disclosed proteins to guinea pigs and the detection of an immune response by means of a skin test (page 373, column 2, under the heading "Sensitization of guinea pigs and skin testing" and Table 3). Nagai et al designates the P32 protein as MPT 44 and it is used in the method of detecting the presence of an immune response as evidenced by the MPT 44 entry in Table 3, thus fulfilling the specific embodiments of claims 22 drawn to the administration of at least one immunodominat epitope which, when given the broadest reasonable interpretation reads on the administration of the full length protein.

16. Claims 11, 14, 17 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Pal et al (Infection and Immunity, 1992, Vol. 60, pp. 4781-4792, reference TR of the IDS filed March 17, 1997). The specific limitations of claims 11, 14 and 20 are set forth above. Claim 17 sis drawn to a method of immunizing a host against an infectious pathogen of the genus Mycobacterium comprising the steps of providing at least one least one immunodominant epitope of at least one majorly abundant secreted extracellular product selected from the group consisting of M tuberculosis 110 KD protein, 80 KD protein, 71 KD protein, 58 KD protein, 45 KD protein,

30 KD protein, 24 KD protein, 23.5 KD protein, 23 KD protein, 16 KD protein, 14 KD protein, and 12 KD protein and respective analogs, homologs and subunits thereof; and introducing said at least one immunodominat epitope to said mammalian host to induce an effective immune response to subsequent infection by said infectious pathogen.

Pal et al disclose a major extracellular M tuberculosis protein having the apparent molecular weight of 68 KD which was found to be the same as the heat shock 71 protein. (Page 4782, second column, lines 10-14 under the heading "Isolation of selected EP" and page 4784, second column, under the heading "Analysis of M tuberculosis EP") The 71 KD protein is identified in the specification on page 34, lines 14-32, as the 71 KD heat shock protein. Therefore the protein with the apparent molecular weight of 68 KD is the same as the claimed 71 KD protein. Pal et al disclose a method for immunizing a guinea pig against subsequent infection by M tuberculosis, said method comprising administering a vaccinating agent comprising the extracelluar proteins of M tuberculosis in incomplete Freund adjuvant or in L pneumophila adjuvant (page 4783, first column, under the heading "Immunization of guinea pigs with EP" and pages 4786-4787, starting in the second column, under the heading "Guinea pigs immunized with EP develop a substantial level of protective immunity to aerosol challenge with virulent M tuberculosis"). Because Pal et al disclosed that the major component of the extracellular proteins was the 71 heat shock protein, it is reasonable to assume that the extracellular proteins administered to said guinea pigs.

17. Claims 11, 14, 20, 23 and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Kingston et al (Infection and Immunity, 1987, Vol. 55, pp. 3149-3154, reference BB of the IDS filed November 13, 1997) as evidenced by Nagai et al (Infection and Immunity, 1991, supra). The limitations of the claims are set forth above.

Kingston et al disclose a method for producing the 14 KD protein of M tuberculosis comprising the steps of transforming E coli with a vector comprising the polynucleotide encoding

the 14 KD protein to form a transformed cell, culturing the transformed cell to produce the 14 KD protein as a fusion protein, and recovering the 14 KD product that is produced by the culturing of the cell (page 3149, under the headings "Phages and bacteria, Preparation of the rTB68 antigen" and "Purification of fusion protein"). Nagai et al disclose a 14 KD protein which is a major protein antigen found in M tuberculosis culture fluid. Thus, the 14 KD protein of Kingston fulfills the specific embodiment of a majorly abundant extracellular protein for the reasons set forth above. Kingston et al disclose a method for detecting the presence of an immune response in a mammal against M leprae comprising administering the recombinant 14 KD protein (page 3150, first column, under the heading "Mouse Immunization", "(i) 50 ug of pure rTB68") and the subsequent measurement of the resultant immun response (page 3151, first column under the heading "Lymphoproliferative response" and page 3150, second column, under the heading "DTH testing").

18. Claims 11, 14, 23 and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhang et al (Molecular Microbiology, 1991, Vol. 5, pp. 381-391, reference BC of the IDS filed November 13, 1997) as evidenced by Abou-Zeid et al (Journal of General Microbiology, 1988, Vol. 134, pp. 531-538). The specific embodiments of the claims are set forth above.

Zhang et al disclose a method for producing the 23 KD protein of M tuberculosis comprising the steps of transforming E. Coli with lambda gt11 library or transforming M smegmantis with a vector comprising the polynucleotide encoding the 23 KD protein, the culturing of the host cell to produce the 23 KD protein, detectable by monoclonal antibodies in the case of lambda gt11 (page 388, under the heading "Immunoassays"). In the case of the host cell of M Smegmatis, the recovery of the protein was evidenced by immunobloting (page 385, figure 4). Thus, Zhang et al disclose the method of producing the 23 KD protein by means of recombinant expression, and the protein produced thereby.

Abou-Zeid et al disclose the 23 KD protein as an extracellular protein of M tuberculosis (Table 1).

19. Claims 11, 14, 23 and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhang et al (Nature, 1992, vol. 358, pp. 591-593) as evidenced by Heym et al (Journal of Bacteriology, 1993, Vol. 175, pp. 4255-4259, reference BE of the IDS filed November 13, 1997) and Nagai et al (Infection and Immunity, 1991, Vol. 59, pp. 372-383). The specific embodiments of the claims are recited above.

Zhang et al disclose a method for producing the catalase-peroxidase protein of M tuberculosis comprising the steps of transforming E coli (figure 2a, lanes 3 and 4). Heym et al discloses the complete gene sequence of the gene encoding the catalase-peroxidase of M tuberculosis, having the molecular weight of 80 KD(Figure 4, and abstract). Nagai et al disclose that the catalase protein is a majorly abundant extracellular protein of M tuberculosis (Table 1).

20. Claims 11, 14, 23 and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Shinnick et al (Infection and Immunity, 1987, Vol. 55, pp. 1718-1721) as evidenced by Abou-Zeid et al (Journal of General Microbiology, 1988, Vol. 134, pp. 531-538). The specific embodiments of the claims are set forth above.

Shinnick et al disclose a method for producing the 12, 14, 19, and 71 KD protein of M tuberculosis and the proteins produced thereby, said method comprising the steps of transforming E coli (Table 1 and figure 2).

Abou-Zeid et al disclose the 12, 14, 19 and 71 KD proteins as extracellular proteins of M tuberculosis (Table 1).

21. Claims 11-16 and 20-25 are rejected under 35 U.S.C. 102(b) as being anticipated by Content et al (WO 91/04272, reference AL of the IDS filed March 13, 1997). The specific embodiments of the claims are recited above.

Content et al disclose the polynucleotide encoding the 32 KD antigen of M tuberculosis, and the amino acid sequence encoded thereby (page 93, lines 4-20, and figure 5) and a method for producing the 32 KD protein in E coli (Example 11, page 95, through Example VI, and the recovery of the expressed protein from said E coli (page 108, sections (b) and Example VII). Content et al specifically disclose the growth temperature of the recombinant cells comprising the 32 KD protein as 28 degrees (page 106, lines 17-21), this fulfilling the specific embodiment of claim 28. Content et al disclose the 32 KD protein or peptides thereof as a vaccine composition (page 63, line 26 to page 64, line 4).

22. Claims 1, 2, 6 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Content et al in view of Pal et al (Infection and Immunity, 1992, Vol. 60, pp. 4781-4792) and the abstract of Collins et al (Abstract of the general Meeting of the American Society for Microbiology, 1993, vol. 93, page 180, abstract U-63) and the abstract of Barr et al (AIDS 9th Annual Meeting, 1992, pages 385-389). Claim 1 is drawn to a vaccinating agent comprising at least a portion of at least one majorly abundant extracellular product selected from the group consisting of M tuberculosis 110 KD protein, 80 KD protein, 71 KD protein, 58 KD protein, 45 KD protein, 30 KD protein, 24 KD protein, 24 KD protein, 23.5 KD protein, 23 KD protein, 16 KD protein, 14 KD protein, 12 KD protein, and respective analogs, homologs and subunits thereof and an adjuvant selected from the group consisting of IL-12 and MF 59. Claim 2 embodies the agent of claim 1, wherein the product is the M tuberculosis 30 KD protein. . Claim 5 embodies the method of claim 1 wherein the adjuvant is a mixture of Il-12 and MF 59.

Claim 6 is drawn to a method for immunizing a mammalian host against an infectious pathogen of the genus Mycobacterium, said method comprising the steps of: providing a

vaccinating agent a comprising at least a portion of at least one majorly abundant extracellular product selected from the group consisting of M tuberculosis 110 KD protein, 80 KD protein, 71 KD protein, 58 KD protein, 45 KD protein, 30 KD protein, 24 KD protein, 24 KD protein, 23.5 KD protein, 23 KD protein, 16 KD protein, 14 KD protein, 12 KD protein, and respective analogs, homologs and subunits thereof and an adjuvant selected from the group consisting of IL-12 and MF 59, and introducing said vaccinating agent into said mammalian host to induce an effective immune response to subsequent infection by said infectious pathogen. Claim 7 embodies the method of claim 6, wherein the product is the M tuberculosis 30 KD protein. Claim 10 embodies the method of claim 6 wherein the adjuvant is a mixture of Il-12 and MF 59.

Content et al teach the polynucleotide encoding the 32 KD antigen of M tuberculosis, and the amino acid sequence encoded thereby (page 93, lines 4-20, and figure 5). Content et al teach the 32 KD protein or peptides thereof as a vaccine composition (page 63, line 26 to page 64, line 4).

Pal et al teach a method for immunizing a guinea pig to induce an effective immune response against M tuberculosis, comprising introducing a mixture of extracellular proteins of M tuberculosis into said guinea pig. Pal et al teach the use of incomplete Freund's adjuvant and L pneumophila adjuvant (page 4783, under the headings "Immunization of guinea pigs with EP", "Studies of protective immunity" and page 4786, under the heading "Guinea pigs immunized with EP develop a substantial level of protective immunity to aerosol challenge..."). It is noted that the mixture of extracellular proteins used by Pal et al contains some 30-32 KD protein (figure 2).

The abstract of Collins et al teaches that mice vaccinated with M smegmatis expressing recombinant proteins of M bovis BCG did not express an increased resistance to a later tuberculosis challenge, while mice vaccinated with M smegmatis suspended in Freund's adjuvant were protected from M tuberculosis aerosol challenge.

The abstract of Barr et al teaches that adjuvants such as MF 59 and MF 59/slow release particles are more potent adjuvants that conventional adjuvants such as alumn, and induce a longer term neutralizing activity of a vaccine against malaria.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to prepare a vaccine comprising the 30 KD protein M tuberculosis with the adjuvant MF 59 and use said vaccine in a method of inducing protective immunity against M tuberculosis. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Content et al and Pal et al on the efficacy of inducing protective immunity by vaccinating with extracellular proteins of M tuberculosis, the teachings of the abstract of Collins et al on increased protection afforded by a vaccine comprising adjuvant versus a vaccine without adjuvant, and the teachings of the abstract of Barr et al on the potency of the MF 59 adjuvant in a vaccine preparation.

23. Claims 1, 2, 4, 6, 7 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Andersen et al (U.S. 5,955,077) in view of Content et al (U.S. 5,736,524). Claim 4 embodies the agent of claim 1 wherein said adjuvant is Il-12. Claim 9 embodies the method of claim 6 wherein said adjuvant is Il-12.

Andersen et al teach a vaccinating agent and a method of vaccinating a mammal comprising the administration of secreted antigens of M tuberculosis comprising molecular weights in the range of 20 to about 32 KD (column 1, lines 56 to column 2, line 3, and column 4, lines 15-16). Anderson et al teach the administration of said antigens with an adjuvant substance and an immune modulating substance, such as Il-12 (column 8, lines 31-60). Anderson et al do not specifically teach the 30 KD and the 32 KD proteins as secreted proteins of M tuberculosis that would be administered within this range of molecular weights.

Content et al teach that protective T-cell antigens are proteins which are secreted by M tuberculosis during residence in macrophage. Content et al teach that these proteins are

recognized as the antigen 85 complex, which is taught by Nagai et al (supra) to comprise the 32A KD protein as the 85A subunit and the 30 KD protein as the 85B subunit (table 1, Nagai et al).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use the antigen 85 complex in a vaccinating agent in a method of inducing protective immunity as taught by Anderson et al. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Content et al on the suggestions by content et al that the antigen 85 complex is a good vaccine target.

24. Claims 1-4 and 6-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Andersen et al (U.S. 5,955,077) in view of Content et al (U.S. 5,736,524) and Nagai et al as applied to claims 1, 2, 4-7, 9 and 10 above, and further in view of the abstract of Alavi et al (Abstracts of the General Meeting of the American Society for Microbiology, 1989, Vol. 89, page 155).

Claim 3 is drawn to the vaccinating agent of claim 1 wherein said at least one majorly abundant protein is a mixture of M tuberculosis 32A protein, 30 KD protein and a 16 KD protein Claim 8 is drawn to the method of claim 6 wherein said at least one majorly abundant protein is a mixture of M tuberculosis 32A protein, 30 KD protein and a 16 KD protein.

The combination of Anderson et al and Content et al and Nagai et al render obvious a vaccinating agent comprising the M tuberculosis extracellular proteins of 30 KD and 32 KD, and a method of vaccination comprising the administration of the combination of said 30 KD and 32 KD proteins for the reasons set forth above. Neither Anderson et al nor Content et al specifically teach a combination of the M tuberculosis extracellular proteins of 30 KD and 32 KD with the 16 KD protein, although Content et al teach that proteins synthesized by M tuberculosis during residence in macrophages are protective T-cell antigens.

The abstract of Alavi et al teaches that the proteins of 16 KD, 20 KD and 40 KD are upregulated by M tuberculosis during phagocytosis, and therefore would be expressed inside macrophage.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to include the 16 KD protein of M tuberculosis with the vaccinating agent in the method of inducing a protective immune responce as taught by the combination of Anderson et al and Content et al and Nagai et al. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Content et al on protective T-cell response elicited by proteins produced by M tuberculosis during residence in macrophage.

25. Claims 1, 2, 4-7, 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Andersen et al (U.S. 5,955,077) and Content et al (U.S. 5,736,524) and Nagai et al as applied to claims 1, 2, 4, 6, 7 and 9 above, and further in view of the abstract of Barr et al (AIDS (Annual Meet), 9th, 1992, pages 385-389). The combination of Anderson et al and Content et al and Nagai et al render obvious the claims 1, 2, 4, 6, 7 and 9 for the reasons et forth in section 20, above. Anderson et al teach the enhancement of the immune response by inclusion of an adjuvant substance, such as alum, in combination with Il-12 (column 8, lines 31-60). Neither Anderson et al nor content et al nor Nagai et al teach the method of vaccinating a mammal comprising the administration of a vaccinating agent comprising MF 59 as an adjuvant.

The abstract of Barr et al teaches that adjuvants such as MF 59 and MF 59/slow release particles are more potent adjuvants that conventional adjuvants such as alumn, and induce a longer term neutralizing activity of a vaccine against malaria.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute the MF59 adjuvant for the alum as taught by Anderson et al. One of ordinary skill in the art would have been motivated to do so with a reasonable

expectation of success by the teachings of the abstract of Barr et al which teaches that longer term immunity to an infectious agent can be induced by substitution of MF59 for alumn.

26. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentable distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g. *In re Berg*, 140 F. 3d 1428, 46 USPQ2d 1226 (Fed Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

27. Claims 11-19 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 14-17 of U.S. Patent No. 5,108,745 in view of Nagai et al (Infection and Immunity, 1991, Vol. 59, pp. 372-383) and Pal et al (Infection and Immunity, 1992, Vol. 60, pp. 4781-4792). Claim 14 of the '745 patent is drawn to a vaccine produced according to the method , said method comprising the steps of : identifying at lest one extracellular product of Mycobacterium tuberculosis which stimulates strong cell mediated immune responses in at least one mammalian host infected with or immune to M tuberculosis, and determining a human protective immunity inducing effective amount of said extracellular product, wherein said extracellular product is m tuberculosis major extracellular protein. Claim 15 of the '745 patent embodies the vaccine of claim 13 wherein said intracellular pathogen is M tuberculosis. Claim 17 of the '745 patent is drawn to a vaccinating agent comprising M tuberculosis extracellular protein. Claim 16 of the '745 patent is drawn to a method for immunizing a human host against subsequent exposure to M tuberculosis comprising the step of immunizing said host with M tuberculosis major extracellular protein.

Nagai et al teach that the antigen 85 complex is a major constituent of M tuberculosis culture fluids (page 372, second column lines 8-10). Nagai et al teach that the 85B subunit of the antigen 85 complex was able to induce a potent delayed type hypersensitivity reaction in guinea

pigs, but the 85A subunit did not evoke a strong DTH. Paul et al (Immunology, (text), 1993, pages 1273-1274, under the heading "Anergy") teaches that DTH reactions elicited by soluble antigens are a function of CD4 T cells, whereas acquired resistance against intracellular bacteria additionally involves CD8 lymphocytes.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use the antigen 85 complex comprising the 30 KD and 32A KD proteins of M tuberculosis in a vaccine and administer said vaccine in a a method for immunizing a human host against subsequent exposure to M tuberculosis comprising the step of immunizing said host with M tuberculosis major extracellular protein. as claimed in the '745 patent One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Nagai et al on the immunogenicity of the antigen 85 complex which is a majorly abundant extracellular protein of M tuberculosis.

28. Claims 1, 2, 4-7, 9 and 10 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 14-17 of U.S. Patent No. 5,108,745 in view of Anderson et al (US 5,955,077) and Content et al (US5,736,524) and Nagai et al (Infection and Immunity, 1991, Vol. 59, pp. 372-383) and the abstract of Barr et al (AIDS (Annual Meet), 9th, 1992, pages 385-389).

Andersen et al teach a vaccinating agent and a method of vaccinating a animals and humans comprising the administration of secreted antigens of M tuberculosis comprising molecular weights in the range of 20 to about 32 KD (column 1, lines 56 to column 2, line 3, and column 4, lines 15-16). Anderson et al teach the administration of said antigens with an adjuvant substance, such as alum and an immune modulating substance, such as Il-12 (column 8, lines 31-60). Anderson et al do not specifically teach the 30 KD and the 32 KD proteins as secreted proteins of M tuberculosis that would be administered within this range of molecular weights.

Content et al teach that protective T-cell antigens are proteins which are secreted by M tuberculosis during residence in macrophage. Content et al teach that these proteins are recognized as the antigen 85 complex, which is taught by Nagai et al (supra) to comprise the 32A KD protein as the 85A subunit and the 30 KD protein as the 85B subunit (table 1, Nagai et al).

Neither Anderson et al nor Content et al nor Nagai et al teach the method of vaccinating an animal or a human comprising the administration of a vaccinating agent comprising MF 59 as an adjuvant. The abstract of Barr et al teaches that adjuvants such as MF 59 and MF 59/slow release particles are more potent adjuvants that conventional adjuvants such as alumn, and induce a longer term neutralizing activity of a vaccine against malaria.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use the antigen 85 complex comprising the 30 KD and 32A KD proteins of M tuberculosis and further comprising MF59 and Il-12 in a vaccine, and administer said vaccine in a a method for immunizing a human host with M tuberculosis major extracellular protein as claimed in the '745 patent. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of the abstract of Barr et al on the higher adjuvanating potency of MF59 versus alum, and the teachings of Anderson et al on a vaccine comprising alum as adjuvant.

29. Claims 1-4, and 6-9 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 14-17 of U.S. Patent No. 5,108,745 in view of Anderson et al (US 5,955,077) and Content et al (US5,736,524) and Nagai et al (Infection and Immunity, 1991, Vol. 59, pp. 372-383) and the abstract of Alavi et al (Abstracts of the general Meeting of the American society for Microbiology, 1989, Vol. 89, page 155).

Andersen et al teach a vaccinating agent and a method of vaccinating a animals and humans comprising the administration of secreted antigens of M tuberculosis comprising molecular weights in the range of 20 to about 32 KD (column 1, lines 56 to column 2, line 3, and

column 4, lines 15-16). Anderson et al teach the administration of said antigens with an adjuvant substance, such as alum, and an immune modulating substance, such as Il-12 (column 8, lines 31-60). Anderson et al do not specifically teach the 30 KD and the 32 KD proteins as secreted proteins of M tuberculosis that would be administered within this range of molecular weights.

Content et al teach that protective T-cell antigens are proteins which are secreted by M tuberculosis during residence in macrophage. Content et al teach that these proteins are recognized as the antigen 85 complex, which is taught by Nagai et al (supra) to comprise the 32A KD protein as the 85A subunit and the 30 KD protein as the 85B subunit (table 1, Nagai et al).

The abstract of Alavi et al teaches that the proteins of 16 KD, 20 KD and 40 KD are upregulated by M tuberculosis during phagocytosis, and therefore would be expressed inside macrophage.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to include the 16 KD protein of M tuberculosis in a vaccinating agent comprising the antigen 85 complex in the method of inducing a protective immune responce in a human, as claimed in the '745 patent. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Content et al on protective T-cell response ilicited by proteins produced by M tuberculosis during residence in macrophage, and the identification of the 16 KD protein as a protein which is expressed by M tuberculosis during phagocytosis. One of skill in the art would recognize that M tuberculosis is undergoing phagocytosis during residence in a macrophage.

30. Claims 11-16 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6-9, 35 and 71-94 of co-pending Application No. 08/156,358 in view of Nagai et al (Infection and Immunity, 1991, Vol. 59, pp. 372-383). Although the conflicting claims are not identical, they are not patentably distinct from each other because the vaccinating agents of claims 6-9 and 35 anticipate the instant

claims to a vaccinating agent or an immunodiagnostic agent comprising the M tuberculosis 110 KD protein, 80 KD protein, 71 KD protein, 58 KD protein 45 KD protein, 32A KD proteins, 32B protein , 23 KD protein, 16 KD protein, 14 KD protein 12 KD protein in light of the teachings of Nagai et al on the components of the antigen 85 complex as indicated in table 1 of Nagai et al. Thus, claims drawn to the 32A and 32B complexes anticipates the instant claims drawn to the 30 KD protein.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

31. Claims 11-16 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 10-16, 33, 34, 36 and 37 of co-pending Application No. 08/156,358 in view of Content et al (WO 91/04272),. The limitations of claims 11-19 are set forth above. As stated supra, the intended use of the claimed proteins does not lend patentable distinctness to the disclosed proteins. This also applied to pending claims 14 and 15 of the '358 application. Further, the origin of the claimed proteins, i.e. whether they are produced synthetically, recombinantly or immunologically, does not influence the nature of the claimed proteins, and therefore does not lend patentable distinctness to the proteins. Accordingly, instant claims 11-16, drawn to a vaccinating agent and a immunodiagnostic agent are obvious over claims 1-5, 10-15, 33, 34 in view of Content et al who teach the amino acid sequence of the claimed 32 KD protein for use as a vaccinating agent against tuberculosis.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

32. Claims 11-19 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-54 of co-pending

Application No. 09/953,457. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-54 anticipate the instant claims 11-16 and claims 55-60 anticipate the instant claims 17-19. The recitation of the amino acid sequences in claims 2-26 do not impart patentable distinctness to the claims as the vaccinating agent comprising the claimed proteins will inherently have the recited amino acid sequences.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

33. All other rejections and objections as set forth in the previous Office action are withdrawn.

Conclusion

34. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella

Karen A. Canella, Ph.D.

Patent Examiner, Group 1642

April 21, 2003